Review Article

The role of nociceptin and orexin in the pathophysiology of psychogenic stress and sepsis: A literature review

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ABSTRACT

The established paradigm of stress axis is not only borne by the hypothalamic-pituitary-adrenal (HPA) axis. There are various "fine-tuners" in the form of neuromodulators whose intricate functioning is under active investigation. Two such neuromodulators, namely nociceptin and orexin are interesting candidates to further evaluate their respective roles and possible cross-talk in due course of stress. In addition, apart from this outlook toward stress, immune stress is also perceived as an impending threat to the physiology and probably implicates the HPA axis in ways that we fail to comprehend with our current crux of knowledge. Sepsis or system inflammatory response syndrome is an exemplary of such an immune stress where the role of the HPA axis has been evidentially supported. An interesting question which arises is how would neurologically perceived stress and sepsis be guided by various neuromodulators. The scope of this review is to evaluate the existing literature where we look at the role of nociceptin and orexin in guiding the complex etiology of stress and sepsis, respectively. Extensive review has suggested, there also might be a hypothetical "cross-talk" between nociceptin and orexin, though this again has to be supported by further investigations.

KEY WORDS: Nociceptin; Orexin; Stress; Sepsis

INTRODUCTION

Stress is a response to cues that tend to compromise our vitality. It mobilises dynamic activities that would be required to sustain our physiology and restore it to its homeostasis. Acute and chronic stress responses are subject to classification, based primarily on the prolongation of exposure to stressors. Stressors are internal and/or external cues evoking physical, psychogenic or immunologic stress responses. This is an interesting premise of investigation and for years has involved the interpretation of such responses from the perspective of different physiologic pathways and molecules. The hypothalamic-pituitary-adrenal (HPA) axis is a key pathway which describes the functional repertoire of stress and has been implicated not only in psychological stressor-induced responses but also inflammatory stress-induced response paradigm.[1]

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Our internal homeostatic milieu is facilitated by the HPA axis[2] whose role is distinctly related with stress. On perceiving a stressor stimuli, the parvocellular neurons of the paraventricular nucleus (PVN) is activated in the hypothalamus to secrete corticotropin-releasing hormone (CRH).[3] Via the hypophyseal portal circulation CRH reaches the anterior pituitary where, on binding with CRH receptor I, induces adrenocorticotropic hormone (ACTH) release by the pituitary corticotropic cells.[4] ACTH reaches

the adrenal cortex through systemic circulation and stimulates the secretion of glucocorticoids. The HPA axis response equips the body to cope with a potential "threat" by mobilizing energy stores and maintaining an aroused state, effective optimally over a short period.[5] Nevertheless, a prolonged persistence of this response causes impairment of normal physiologic, immunologic, and psychological/cognitive functions.[6] Thus, this system is also equipped with associated feedback and feedforward responses, where the circulating levels of glucocorticoids determine when the repertoire requires a central suppression. Glucocorticoids inhibit their own production by this feedback mechanism, by inhibiting the release of ACTH from the pituitary gland and the CRH from the PVN in the hypothalamus.[7] In addition, they also have other central targets including the limbic system, where they act to integrate HPA functions in concert with the PVN.[8]

In rats and humans, GCs display a circadian secretory pattern, with highest levels during the active phase for both species (day in the case of man and night for rodents) and lowest in the hours of least activity (sleeping phase).[9] Such diurnal and nocturnal biorhythms of hormone secretion are found to be regulated by a central oscillator located in the anterior hypothalamus, the suprachiasmatic nucleus (SCN), which uses environmental cues to regulates GC secretion, via the HPA axis and the autonomic nervous system.[10,11] Underlying this circadian rhythm, endogenous GC secretion exhibits an ultradian rhythm, characterized by hourly pulses which vary in amplitude over the 24-h period.[12,13] The activity of the HPA axis is sensitive to physiological, pharmacological, or psychological disruption. At times of acute physical or psychological stress, there is increased activity at every level of the HPA axis leading to increased responses from its peripheral and central targets. This further helps attain homeostasis after the stressful situation by facilitating behavioral adaptations or physiological adaptations including attenuation of the stress response and suppression of pro-inflammatory cytokines.[14] In chronic inflammatory stress models of adjuvant-induced arthritis in rats, a hyperactive HPA axis is observed, with increased ACTH release from the pituitary.[15] Patients suffering from major depression also have increased HPA axis activity, leading to enhanced secretion of cortisol and increased pituitary and adrenal volume in some cases.[6,16] In some cases, dysregulated HPA axis may arise from early-life psychological or physical stress.[17] Furthering this knowledge, dysregulation of the HPA axis (at any level) in enunciating an immunologic overdrive has also be seen in systemic inflammatory response syndrome (SIRS) or sepsis.[18,19] Yet, what is not understood completely is how this response is mediated.

Apart from psychological stress, the role of HPA axis has also been elaborately discussed in the context of an overwhelming inflammatory response known as SIRS. SIRS is an extreme imbalance and an established stressor. Where physical trauma or an infection results in localized cardinal signs of inflammation followed by immune responses, SIRS is a systemic dissemination of inflammation. SIRS from infection is termed as sepsis. Characteristic pathology of this syndrome is marked by hypo/hyperthermia, hemodynamic, and microvascular changes such as fluctuating blood pressure, hypoperfusion, coagulopathy, acidosis and cardiac dysfunction with kidney and respiratory failure on severity. Septic shock, an often common case of critical care mortality is marked by the mentioned symptoms of sepsis, along with disseminated intravascular coagulopathy and multi-organ dysfunction. Sepsis puts the body under an imbalance of pro-inflammatory and anti-inflammatory responses.[20] Apart from the described clinical pathophysiology, the underlying cause to the symptoms are mediated by an elaborate confluence of multiple cytokines, such as interleukin (IL-1β), TNF-α, and IL-6; prostaglandins, kinins, acute phase proteins, and various proteins of the complement system like C5a which help shaping the immune response in its totality.

The role of endogenous glucocorticoids in modulating behavioral, as well as inflammatory stress responses, aims at restoring the body to its basal homeostasis under events of challenge. In autoimmune inflammatory disorders such as rheumatoid arthritis, inflammatory bowel disorder, and multiple sclerosis, an impaired HPA axis has been implicated in respective animal model studies. Psychiatric disorders have also been shown to exacerbate inflammatory states in studies performed with depression or PTSD. Furthering this knowledge of a dysregulated HPA axis response (at any level) in enunciating an immunologic overdrive can also be seen in SIRS or sepsis. It has been observed in untreated Sprague Dawley rats and their (cecal ligation puncture [CLP] to induce sepsis) procedure performed littermates that over a 48 h observation period, there were increased levels of corticosterone (CORT) and decreased levels of ACTH in the blood plasma, for the first 24 h.[21] This changed at 48 h with increased ACTH and decreased CORT, suggesting at a possible discrepancy in the HPA axis response. In a separate study, serum cortisol levels were correlated with mortality incidence in patients.[22] Higher levels of serum cortisol (measured during morning hours) could possibly be associated with mortality over a 90-day period.[22] Owing to a dysregulated HPA axis, it has also been seen that the interaction between the adrenal gland and the immune system contributes toward dissociation between the levels of circulating cortisol and ACTH.[23] Glucocorticoid resistance has been cited as an effect of circulating cytokines, which may result in decreased binding capacity of the glucocorticoids with glucocorticoid receptors (GCR), due to the formation of GCR complexes with pro-inflammatory transcription factors like AP-1 and NF-κB.[24,25] Thus, in a clinical study performed with patients, treatment with hydrocortisone in low dosage seemed to alleviate mortality incidence in patients with septic shock.[26]

It is an attempt at unraveling possible unexplained areas entailing two neuromodulators, orexin, and nociceptin, to look into their respective effects on the HPA axis, psychological stress, and sepsis-related stress responses.

OREXIN/HYPOCRETIN AND ITS ROLES IN THE STRESS RESPONSE

Hypocretins/orexins is a neuromodulator discovered in the late 90s.[27,28] These novel ligands for orphan G-protein coupled receptors (GPCRS) were secreted from cell bodies located in the lateral hypothalamus[28] which is known to regulate our food intake. Hypocretins are of two types: Orexins A and B. Orexin A is 33 amino acid long and has two intrachain disulfide bonds while Orexin B is a linear 28 amino acid residue peptide. The two categorized orexin receptors are OX1R and OX2R which belong to the superfamily of GPCRS Gq, Gi/0, Gs and G12/13.[28] Orexinergic neurons were widely distributed in lateral hypothalamus, perifornical area, and dorsomedial hypothalamic nucleus with their projections widely sent throughout the nervous system like the amygdale, bed nucleus of stria terminalis, and hippocampus.[29] Roles of orexin neuropeptides have been described by researchers over the years, including their function in reward and stress systems of our body.[30-32] It was also suggested that hypocretins are involved in narcolepsy, a neurological disorder characterized by a primary disorganization of the sleep-wake cycle, shown through a canine model of the disorder.[33]

Noradrenergic, sympathetic and parasympathetic systems of our body interact with the HPA axis in regulating cardiovascular tone, respiratory rate, and intermediate metabolism by the help of corticosteroids paving the path for the body to undergo a cascade of events for response to stress.[34] Just as the HPA axis prepares the body for response to stress by increasing the cardiac and respiratory response, it was observed that orexin activates monoaminergic and cholinergic neurons in the hypothalamus and brain stem regions to maintain wakefulness.[35] Such a response was triggered if accompanied by conditions of hypoglycemia induced by starvation as observed in an experiment in mice where an orexin gene knockout mouse failed to response to hypoglycemic conditions. While a wild-type starved mouse responded with greater alertness and appeared motivated to find food.[36] In this case, starvation and hypoglycemic condition can be termed as a stressor and the stress response was carried out with the help of orexinergic pathway responsible for food intake and motivation/reward, namely the locus ceruleus region of the lateral hypothalamus where the orexinergic neurons are found in abundance.

Consequently, it was found that central orexin/hypocretin activates hypothalamo-pituitary adrenal (HPA) axis and may be involved in stress-induced activation of the HPA axis by studying plasma levels of corticosteroids after intracerebroventricular (I.C.V) administration of both Orexins A and B.[37] Following this, another research group using CORT expression as the measurement of CORT in blood, failed to find a significant rise in the same with I.C.V administration of Orexin A in neonatal chicks putting a question to the relationship between the HPA axis and the orexinergic system.[38] Until recent times where the administration orexin antagonists were seen to reduce stress responses in morphine or opiate withdrawn mice using c-Fos expression in the nucleus accumbens (NAc) shell, bed nucleus of stria terminalis, central amygdala, and hypothalamic PVN, but did not modify the HPA axis.[39] This shows the critical role played by the orexinergic system in brain stress system, particularly in the limbic system with or without the intervention of the HPA axis. Further in support of this proposition, it has been seen that Orexin A infusion in NAs increases feeding behavior in mice model subjected to starvation stress.[40] Thus, orexins play an important role in modulating stress signals mainly in the limbic system but whether it is directly influencing or choosing the HPA axis as the mediator in the stress response remains to be an unsolved mystery.

NOCICEPTIN/ORPHANIN FQ AND ITS ROLE IN STRESS RESPONSES

Nociceptin was identified by virtue of deorphanization of GPCR.[41] Its effects have been elicited as pain sensation, drug dependency and rewarding properties of the same, and in the pathophysiology of stress and depression. Centrally, while it controls the cardiovascular responses, peripherally, it has been shown to dictate many key aspects of the various systems.[42] Nociceptin is present all around the brain. Even though the nociceptin receptor (NOP) is found to have structural similarity with the general opioid GPCR, it is seen that it has minimal binding capability with the opioid receptor as such. However, in the cellular level, the signaling cascades are same as that of any opioid receptor mediated cascade actions. Here, we will extensively focus on its anxiolytic actions in two very different stress systems and won't delve into the detailed pathophysiology of its role in hyperalgesia, allodynia,[43] circadian rhythmicity.[44] The NOP shares a conserved homology in human and mouse variants of the same gene.[45] Its ligand, the endogenous nociceptin/orphanin FQ (N/OFQ) is 17 amino acid long and has resemblances with the endogenous ligand of the kappa opioid receptor dynorphin. The anatomical distribution of NOP/OFQ receptor ligand system has been observed in; cortex, amygdale, hippocampus, pontine nuclei, central gray, lateral septum, anterior olfactory nucleus, raphe complex, locus coeruleus, substantia nigra, interpeduncular nucleus, and the spinal cord,[46] therefore, clearly suggesting that nociceptin plays significant roles in the stress responses.[47] Nociceptin gained the recognition as a potent neuropeptide that was not restricted only in the central nervous system but had far

reaching consequential effects on the cardiovascular system, the immune system, the gastrointestinal tract, respiratory system and the urogenital system.[42]

Nociceptin contributes to the synthesis and release of other major hormones or peptides that exert excitatory effects on the HPA axis. In fact, OFQ/N-induced activation of the HPA axis is accompanied by upregulation of CRH mRNA in the PVN of the hypothalamus and increased expression of POMC mRNA in the pituitary.[48] Moreover, I.C.V administration of OFQ/N reportedly increased Fos protein expression in the PVN.[49] However, given that OFQ/N binding to NOP-R reduces neuronal excitability, inhibiting both glutamate and GABA release,[50-52] it is likely that activation of PVN neurons in response to OFQ/N occurs through indirect mechanisms. It has been suggested that OFQ/N may drive HPA axis output by disrupting limbic feedback to the hypothalamus.[48,53] It is recognized that the hippocampus expresses high levels of GR, and this serves as a major source of glucocorticoid-mediated feedback control over HPA axis output.[54] Stress-induced elevation of CORT gene (marker for corticosteroid in the blood), and thus, the synthesis of glucocorticoid serve to mobilize energy stores and increase arousal. In this way, glucocorticoids are beneficial for short-term survival as they prepare animals to cope with real or perceived threats to homeostasis. However, prolonged exposure to glucocorticoids can suppress normal immune function and impair cognition. Notably, circulating glucocorticoids provide feedback inhibition that is mediated, in part, by limbic-associated structures.[55,56] Specifically, while there are multiple levels of glucocorticoid feedback, binding of CORT to GCR in the hippocampus contributes to the inhibitory regulation of HPA axis activation.[57] Thus functional activation of central N/OFQergic pathway may have an important role in the fine-tuning of the acute stress response. Exposure of rats to acute restraint stress increases OFQ/N release in the hippocampus in an adrenal-dependent manner, and mimicked by CORT injection, suggesting that glucocorticoids are necessary for stress-induced hippocampal OFQ/N release.[58] It has been suggested that both the stimulatory effects of OFQ/N on glucocorticoid release and CORT-mediated negative feedback instruction arise from modulation of circadian inputs to the HPA axis.[59,60] In rodents, blood CORT concentrations are lowest during the light or diurnal phase of the circadian cycle, and peak in the nocturnal phase, when rodents display high levels of activity, including increased food and water intake. A critical structure in the regulation of circadian rhythms is the SCN of the hypothalamus, which relays photic information from the retina to the PVN. Interestingly, NOP-R is prominently expressed in the SCN, and OFQ/N has been shown to alter the activity of SCN neurons both *in vitro* [61] and *in vivo*.[44] For example, I.C.V administration of OFQ/N suppressed light-induced c-Fos expression in the SCN of rats,[44] while OFQ/N inhibited both excitatory and inhibitory neurotransmission in SCN neurons.[61] In view of these findings, it has been hypothesized that OFQ/N might stimulate the HPA axis and enhance endocrine, cardiac, and behavioral responses to acute stress by altering circadian input to the PVN across the light/dark cycle.

OREXIN AND NOCICEPTIN IN SEPSIS

There have been very contradictory experimental results to identify the role of orexin in sepsis and septic shock. Initially, it was shown that Orexin A levels in the plasma tend to increase in patients inflicted with sepsis and a reason cited for the same were hypermetabolic and tissue hypoxic stresses.[62] In the following years, a very different study came to reveal very different roles of orexin in sepsis physiology. Cecal-ligation-puncture is an experimental induction of sepsis in model organisms like mouse. In a recent study conducted by Dr. Deutschman and his group showed that, following an induced sepsis procedural technique, a six-fold decrease in the orexinergic activity was observed. This was coupled with decrement in heart rates, respiratory parameter, temperature alleviation, etc. Although pituitary activity increased in the first 24 h after induction of sepsis, the activity gradually decreased after a 48 h observation study.[63] Injection of Orexin A seemed to produce effects after about 49 h indicating that it has importance in the management of sepsis pathogenesis and the effect on the gross functional physiology control centers in the central nervous system. Dr. Deustchman's previous studies and these recent findings have put into view that, treatment to sepsis and mainly focussing on prevention of systemic dysfunction could be the cardinal center of attention. Sepsis treatment fails in almost as much as 80% of cases due to inability of treating the cause of sepsis and its auxiliary actions on the body with equal efficiency. As restoring the body to its homeostasis is more important to continue treatment, application of antibiotics along with alternative drugs that would act to correct the misbalanced functioning of the body have been supported, where he clearly emphasizes on the role of orexin infusion centrally, as a probable curative measure. The question here more so highlights the fact, why and how do orexinergic activities take a dip in the pathogenesis of sepsis?

NO/OFQ, NOP receptor, and NOP antagonist University of Ferrera peptide-101 (UFP-101) have been used to show the effect of NO/OFQ-NOP system in the modulation of immunological stress response. Bacterial endotoxin, lipopolysaccharide (LP) is associated with a significant attenuation of NOP mRNA in the basal forebrain at 4 h of administration, possibly as a compensatory response to increased N/OFQ release, indicating that the endogenous NOP system is involved in the acute HPA axis response to immune challenge. A range of inflammatory stimuli including mitogens, CRH, and pro-inflammatory cytokines, all increase endogenous N/OFQ secretion by immune cells in culture and that N/OFQ itself may serve anti-inflammatory actions involving suppression of IL-2.[64] In a

separate study, LPS which is also known to induce sepsis, was used to treat mice, along with the NOP antagonist UFP-101 and suitable controls. It was shown that the levels of CORT were significantly decreased, further supplemented by concomitant decrement in POMC and ACTH mRNA in a time-dependent manner. Although external injection of NO/OFQ did not exhibit similar effects, this study held a premise to develop on yet unexplored areas of how can nociceptin neuromodulatory system function in the context of systemic inflammation and modulation of the HPA axis.[60] Nevertheless, in a previous experiment, the same group showed the possibility of N/OFQ playing a role in increased CORT levels in blood of plasma mice who were treated with nociceptin, where UFP-101 could counter this effect. An observed flaw of this study remained in the absence of an induced "stress" to the animals used.[48] This could be the reason in the inconsistencies found in these consecutive studies performed by the same group. The expression of N/OFQ increases in the leukocytes (mediators of inflammatory and immune responses) of septic subjects. These circulatory leukocytes become the delivery agents to various compartments of the body, eliciting cardiovascular change and related modifications.[65] In a study of a cohort of patients admitted to the Intensive Care Unit and diagnosed with sepsis had shown modulated effects on the N/OFQ system.[66] In the first 2 days after ICU admission, plasma concentration of nociceptin were elevated while NOP mRNA content was decreased in the said subjects compared to healthy volunteers. As the role of nociceptin receptors was implicated in previous studies, it was evident that downregulating the NOP could be a possible treatment procedure to curb the manifestation of sepsis in the body, which had been proved by injecting nociceptin antagonist UFP-101 in a model animal sepsis study.[67]

Neuroanatomical studies have also suggested how the two neuropeptides in question can have a possible link in the pathogenesis of any possible stress system (two very opposite stress provocation have been cited previously), it is important to put anatomical evidence of nociceptin and orexin regulation or vice versa. This was a study to observe stress-induced analgesia (SIA) in mouse models. It was shown that N/OFQ and Hcrt modulated coordinately the progress of nociception in SIA.[68] This was the study where neuroanatomical evidence was obtained by virtue of immunoreactivity studies. N/OFQ cells were observed in the lateral hypothalamus, and it was dorsally located in the area that had high distribution of Hcrt immunoreactive neurons. It was also seen that both these neuropeptides did not have the same neuron of localization; upholding the high chances of these two kinds of neuropeptide producing neurons forming a local circuitry. On further electron microscopic studies, this plausibility was also proved when immunolabeled N/OFQ axon terminals showed synaptic connections with Hcrt immunolabeled neuronal dendrites in the rat brain.[68]

CONCLUSION

While extensive research has separately seen the role of neuromodulators orexin and nociceptin in psychogenic stress systems and sepsis, it would be interesting to further research where the role of both of these are investigated in the same model system. For example, if an N/OFQ and/or NOP knockout system is created to study the activity of orexin (and vice versa) in stress response we may come on a more definitive pathophysiological explanation of how these response mechanisms are modulated and mediated. As evidence has suggested, there also might be a hypothetical "cross-talk" between nociceptin and orexin, though this again has to be supported by further investigations. Models of sepsis like CLP may also be performed in animal models which have been subjected to psychogenic stress. Following this, studies may focus to look at nociceptin, orexin, and their related receptor function. This may ideally give us an insight into severity (or not) of physiological responses to systemic inflammation, when the animal is subject to chronic psychogenic stress. This opens up an exciting avenue for newer and innovative drug target identification which might aid in alternative treatment options to stress and sepsis. Further investigation and scientific evidence would be required to justify and theory these proposed areas of research.

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